AWARD NUMBERS: W81XWH-14-1-0555

TITLE: Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

PRINCIPAL INVESTIGATOR: **Dr. Arul M. Chinnaiyan**

RECIPIENT: The University of Texas MD
Anderson Cancer Center

Houston, TX 77030

REPORT DATE: DEC 2018

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
DEC 2018	Final	22 Sep 2014 - 21 Sep 2018

4. TITLE AND SUBTITLE

Development of Personalized Cancer Therapy for Men with Advanced Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-14-1-0555

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Nora M. Navone, M.D., Ph.D.
Arul Chinnaiyan, M.D., Ph.D.

E-Mail: nnavone@mdanderson.org and arul@med.umich.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

The University of Texas
MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030-4009

University of Michigan
1400 E. Medical Center Drive
Room 5316 CC
Ann Arbor, MI 48109-5940

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT. Bone metastases typically develop in patients with advanced prostate cancer (PCa). We have previously reported that the fibroblast growth factor (FGF) axis is implicated in the pathogenesis of PCa bone growth, and that FGFR blockade has clinical activity in advanced PCa and bone metastases.[2] In an RNA sequencing study of human PCas we found that different samples express different FGFR1 transcripts. We then mined TCGA PCa database to determine the expression profile associated with two well-characterized FGFR1 splice variants, alpha and beta, which represent the most abundant protein coding transcripts found in PCa. We discovered that each isoform is associated with the expression of different genes. Also, in gene set enrichment analysis, we found that FGFR1 beta (but not alpha) is associated with many different pathways. In particular, FGFR1 beta is significantly associated with MAPK signaling cascade, signaling by FGFR in disease, and pathways in cancer, among others. *In vitro* studies of FGF signaling activation in PCa cells expressing FGFR1 isoforms alpha, beta, or empty vector (EV) confirmed these results. Therefore, these results suggest that FGFR1 alpha and beta induce different genes. Importantly, when compared to PCa cells expressing EV, PCa cells expressing FGFR1 isoforms produce significantly more metastasis and reduced survival of mice injected intracardially with the cells. In summary, our studies suggest that FGFR1 alpha and beta activate different genes and pathways in PCa cells, thus conferring different phenotypes. We further propose that FGFR1 expression in PCa cells favors its metastatic dissemination to bone, and this may be mediated at least partially by activating PCa cell-bone cell interaction. Our studies provide the framework to move forward with clinical trials targeting FGFR in men with advanced PCa.

15. SUBJECT TERMS

Bone metastases, targeted therapy, prostate cancer

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
Unclassified	Unclassified	Unclassified	Unclassified	33	USAMRMC

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Final Report

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1. INTRODUCTION

Castration-resistant progression and bone metastasis are hallmarks of advanced prostate cancer, for which there is no cure. Recent clinical trials have had encouraging results but only in subsets of patients, and emergence of treatment resistance is inevitable for most patients. Thus, strategies for selecting patients who are responders to treatment and for identifying effective combination therapies are urgently needed. The purpose of this study was to develop a strategy for identifying molecular markers of the response of advanced prostate cancer to specific therapies. To achieve this goal, we used clinically relevant prostate cancer patient-derived xenografts (PDXs). We identified genomic alterations in these PDXs. The MD Anderson and Michigan Center for Translational Pathology (MCTP) teams interacted closely to analyze genomic analysis results to generate a responder ID profile hypothesis. The validity of the responder ID profiles will be assessed in clinical trials.

2. KEYWORDS

Bone metastases, targeted therapy, prostate cancer

3. ACCOMPLISHMENTS

What were the major goals of the project?

Specific Aim 1: Develop PDXs that reflect the lethal form of prostate cancer.

Major Task 1: Develop clinically relevant prostate cancer xenografts and comprehensively characterize the xenografts and human donor tumors.

Subtask 1: Establish new and expand existing prostate cancer PDXs from bone metastases or primary tumors.

Subtask 2: Assess the histopathologic and immunohistochemical characteristics of prostate cancer xenografts and human tumors of origin. Assess the fidelity to the human tumor of origin of currently available and newly developed (Subtask 1) PDXs derived from primary prostate cancer or bone metastases.

Specific Aim 2: Develop a responder ID profile hypothesis according to the treatment responsiveness of fully characterized prostate cancer PDXs.

Major Task 2: Identify prostate cancer PDX responders and nonresponders (primary resistance) to treatment with specific drugs and establish treatment-resistant PDX lines.

Subtask 1: Identify prostate cancer PDX responders and nonresponders (primary resistance) to abiraterone plus enzalutamide and establish PDX lines resistant to abiraterone plus enzalutamide (acquired resistance).

Subtask 2: Identify prostate cancer PDX responders and nonresponders (primary resistance) to cabozantinib and develop cabozantinib-resistant PDX lines (acquired resistance).

Subtask 3: Identify prostate cancer PDX responders and nonresponders (primary resistance) to dovitinib and develop dovitinib-resistant PDX lines (acquired resistance).

Major Task 3: Perform integrative genomic analysis of responder as well as primary and secondary treatment-resistant prostate cancer PDXs.

Subtask 1: Send flash-frozen specimens of responder and primary and secondary treatment-resistant prostate cancer PDXs and normal DNA obtained from human donor tumors to the MCTP for whole-genome and transcriptome sequencing (RNA-seq) and for targeted whole-exome sequencing.

Subtask 2: Perform data analysis to identify a list of genomic alterations deemed clinically relevant.

Subtask 3: Identify potential pathways of resistance that can be targeted in combination trials based on clinically relevant genomic alterations in therapy-responsive and -resistant prostate cancer PDXs.

Subtask 4: Subject prostate cancer PDXs to therapies targeting pathways identified in Subtask 3 in combination with abiraterone and enzalutamide, cabozantinib, or dovitinib, giving priority to drugs currently in prostate cancer clinical trials at MD Anderson or the University of Michigan.

Subtask 5: Generate a responder ID profile. The profile hypothesis proposes a link between therapy responses (responder or nonresponder) of prostate cancer PDXs and the identified clinically relevant genomic alterations. The hypothesis will be tested in Specific Aim 3.

Specific Aim 3: Validate the responder ID profile hypothesis in a clinical trial.

Major Task 3: Test this hypothesis by analyzing bone biopsy specimens and/or bone marrow aspirates obtained from sites with bone metastases in patients enrolled in the clinical studies listed in the grant.

Subtask 1: Assess the presence of genomic alterations that define the responder ID profile hypothesis in FFPE bone marrow core biopsy specimens and/or bone marrow aspirates (soluble fractions) obtained before and/or after 8 weeks of treatment.

- Abiraterone and enzalutamide clinical study (NCT01650194; PI, C. J. Logothetis). Three arms: enzalutamide combined with abiraterone (n = 20), enzalutamide (n = 20), and abiraterone (n = 20).
- Cabozantinib clinical study (NCT00940225; PI, P. Corn). N = 21.
- Dovitinib clinical study (NCT00831792; PI, P. Corn). N = 40.

Subtask 2: Examine the results of the bone biopsy specimen and/or bone marrow aspirate analysis (performed by our collaborating statistician, Dr. Broom, in a close interaction with Drs. Navone, Logothetis, Araujo, Troncoso, and Chinnaiyan) to determine whether the patients' responses to therapy were predicted by our responder ID profile hypothesis.

What was accomplished under these goals?

Major Task 1*:* As mentioned, when we were in the process of performing our studies at the MD Anderson site, we were informed that there was a miscommunication between MD Anderson and USAMRMC Animal Care and Use Review Office (ACURO) and that the animal protocols had not been reviewed by ACURO. We were thus asked to stop all studies and return all funds utilized thus far for the project, as this could not be executed until the animal protocol was approved by ACURO. In May 2016, we had our animal protocol approved and we started our studies. We thus started our project by developing new prostate cancer PDXs derived from the prostate and bone metastases. The specific objective was to have

a panel of PDXs that would reflect human prostate cancer so that they can be utilized for our preclinical studies. However, given that PDXs derived from prostate cancer have a slow growth rate, for the proposed studies we used PDXs previously established in our laboratory. Nevertheless, we continued to develop new PDXs, which will now be made available to the scientific community through a material transfer agreement. **Table 1** outlines the tumor tissue implanted in mice for PDX development since May 2016. Table 1 also outlines the status of the implanted tissue (growing, failed, or PDX established).

For the preclinical studies we selected prostate cancer PDXs derived from bone metastases (MDA PCa 118b and MDA PCa 183) and primary prostate cancer (MDA PCa 180-30 and MDA PCa 149-1) for which we have assessed the fidelity with the human tumor of origin.

Table 1. Prostate Cancer Tissue Specimen Implanted into Mice for PDX Developed Since May 2016

Date of tissue implantation in mice	Patient Number	Clinical Stage	Human Donor Tumor Information			PDX Information		
			Procedure Type	Pathology Diagnosis	Tumor Site	PDX Name (MDA PCa)	Current Passage	PSA
5/23/16	327	Metastatic	Biopsy	Metastatic adenocarcinoma	Bone marrow	327-1	Stop growing/Failed	
			Venipuncture	N/A	CTC	327-2	5	68
6/9/16	328	Primary	Venipuncture	N/A	CTC	328-0	Stop growing/Failed	
			Transurethral Resection	Small cell carcinoma with neuroendocrine differentiation	Prostate	328-1	Stop growing/Failed	
						328-3	5	79
						328-5	5	70.33
7/5/16	329	Primary	Radical Prostatectomy	Adenocarcinoma	Prostate	329-9	2	Pending
7/20/16	330	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Bone	330-A	Stop growing/Failed	
7/29/16	331	Metastatic	Biopsy-Core	Atypical cells	Bone	331-A	Stop growing/Failed	
8/17/16	332	Metastatic	Biopsy-Core	Carcinoma	Liver	332-B	Stop growing/Failed	
9/2/16	333	Locally Advanced	Resection	Adenocarcinoma	Soft tissue	333-1	2	Pending
9/2/16	334	Metastatic	Venipuncture	N/A	CTC	334-1	Stop growing/Failed	
9/9/16	335	Metastatic	Venipuncture	N/A	CTC	335-1	Stop growing/Failed	
9/13/16	336	Locally Advanced	Biopsy-Core	Adenocarcinoma	Soft tissue	336-A	stop growing/Failed	
10/3/16	337	Metastatic	Biopsy-Core	Metastatic carcinoma with neuroendocrine differentiation	Liver	337-A	5	62
10/11/16	338	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Bone	338-B	Stop growing/Failed	
10/11/16	339	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Lymph node	339-A	Stop growing/Failed	
10/14/16	340	Metastatic	Biopsy-Core	Metastatic carcinoma	Bone	340-A	Stop growing/Failed	
10/17/16	341	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Pelvic lymph node	341-A	Stop growing/Failed	
		Metastatic	Biopsy-Core	Metastatic Adenocarcinoma	Pelvic lymph node	341-B	Stop growing/Failed	

10/19/16	342	Metastatic	Biopsy-Core	Malignant epithelioid and spindle cell neoplasm with osteoid differentiation	Pelvic soft tissue	342-B	5	41
10/26/16	343	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Retro-peritoneal lymph node	343-A	Stop growing/Failed	
11/18/16	344	Metastatic	Venipuncture	N/A	Blood	344-A	Stop growing/Failed	
12/12/16	345	Metastatic	Biopsy-Core	Metastatic Adenocarcinoma	Paraaortic lymph node	345-A	Stop growing/Failed	
12/20/16	346	Metastatic	Biopsy-Core	Metastatic moderately differentiated adenocarcinoma	Liver	346-A	5	51.67
1/20/17	347	Metastatic	Biopsy-Core	Metastatic high-grade adenocarcinoma	Liver	347-A	Stop growing/Failed	
		Metastatic	Biopsy-Core	Metastatic high-grade adenocarcinoma	Liver	347-B	Stop growing/Failed	
1/27/17	348	Locally Recurrent	Transurethral Resection	High-grade adenocarcinoma	Bladder	346-1 and 3	Stop growing/Failed	
2/3/17	349	Metastatic	Biopsy-Core	Metastatic poorly differentiated carcinoma	Adrenal grand	349-A and -B	Failed	
2/6/17	350	Metastatic	Biopsy-Core	Poorly differentiated malignant neoplasm	Prostate	350 a+B	3	
2/7/17	351	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Liver	351-A and -B	Failed	
2/10/17	352	Metastatic	**Lymph Node Dissection**	Metastatic Adenocarcinoma	Lymph node	352-1	4	121
			Lymph Node Dissection	Metastatic Adenocarcinoma	Lymph node	352-8	5	63.33
			Lymph Node Dissection	Metastatic Adenocarcinoma	Lymph node	352-14	3	Pending
2/17/17	353	Metastatic	Biopsy-Core	Metastatic adenocarcinoma	Lymph node	353 A+B	Failed	
2/27/17	354	Metastatic	Lymphadenectomy	Metastatic adenocarcinoma	Lymph node	354-3	Failed	
			Lymphadenectomy	Metastatic adenocarcinoma	Lymph node	354-5	Failed	
			Lymphadenectomy	Metastatic adenocarcinoma	Lymph node	354-7	Failed	
3/14/17	355	Metastatic	Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Rectum	355-3	5	34.67
			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Rectum	355-6	5	35.33
			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Bladder	355-9	5	30.67
			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Bladder	355-12	5	51.67

			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Lymph node	355-15	5	28.33
			Cystectomy	Adenocarcinoma with predominately sarcomatoid and small cell components	Lymph node	355-18	4	28
4/4/17	356	Metastatic	Lymph Node Dissection	Metastatic adenocarcinoma	Lymph node	356-3	5	32.67
4/18/18	357	Locally Advanced	Resection	Adenocarcinoma	Pelvic mass	357-1	3	Pending
4/25/17	358	Metastatic	Bone Marrow Biopsy	No tumor present	Bone marrow	358-A	2	Pending
5/2/17	359	Metastatic	Prostatectomy	Adenocarcinoma	Prostate	359-11	Failed	
5/4/17	360	Locally Advanced	Prostatectomy	Adenocarcinoma	Prostate	360-15	2	Pending
6/12/17	361	Metastatic	Venipuncture	N/A	Blood	361A + B	Failed	
6/12/17	362	Metastatic	Biopsy-Core	Atypical Cells and Stromal Fibrosis	Prostate	362A+ B	Failed	
7/14/17	363	Primary	Prostatectomy	Adenocarcinoma	Prostate	363-10	2	Pending
8/25/17	364	Metastatic	Craniotomy	Pending	Brain	364-1	Failed	
			Craniotomy	Pending	Brain	364-5	2	Pending
9/22/17	365	Metastatic	Biopsy-Core	Poorly Differentiated Carcinoma	Liver	365-A	Failed	
1/25/18	366	Metastatic	TURP	Adenocarcinoma	Prostate	366-1	Failed	
						366-3	Failed	
2/27/18	367	Metastatic	Biopsy-Core	Adenocarcinoma	Prostate	367-A+B	Failed	
4/19/18	368	Metastatic	Venipuncture	N/A	CTC	368-1	0	
5/2/18	369	Metastatic	Venipuncture	N/A	CTC	369-1	1	Pending
5/3/18	370	Metastatic	Venipuncture	N/A	CTC	370-1	0	
5/3/18	371	Metastatic	Venipuncture	N/A	CTC	371-1	0	
5/3/18	372	Metastatic	Venipuncture	N/A	CTC	372-1	0	
5/10/18	373	Metastatic	Venipuncture	N/A	CTC	373-1	0	
5/17/18	374	Metastatic	Venipuncture	N/A	CTC	374-1	0	
5/24/18	375	Metastatic	Venipuncture	N/A	CTC	375-1	0	
5/24/18	376	Metastatic	Venipuncture	N/A	CTC	376-1	0	
5/25/18	377	Metastatic	Craniotomy	Adenocarcinoma	Brain	377-1	0	
						377-4	1	Pending
						377-7	0	
						377-9	0	
5/25/18	378	Metastatic	Venipuncture	N/A	CTC	378-1	Failed	
5/29/18	379	Metastatic	Venipuncture	N/A	CTC	379-1	0	
5/31/18	380	Metastatic	Venipuncture	N/A	CTC	380-1	0	
5/31/18	381	Metastatic	Venipuncture	N/A	CTC	381-1	0	
6/7/18	382	Metastatic	Venipuncture	N/A	CTC	382-1	0	

6/25/18	383	Metastatic	Venipuncture	N/A	CTC	383-1	0	
6/28/18	384	Metastatic	Venipuncture	N/A	CTC	384-1	0	
6/29/18	385	Metastatic	Venipuncture	N/A	CTC	385-1	0	
7/2/18	386	Metastatic	Venipuncture	N/A	CTC	386-1	0	
7/5/18	387	Metastatic	Venipuncture	N/A	CTC	387-1	Failed	
7/12/18	388	Metastatic	Venipuncture	N/A	CTC	388-1	0	
7/16/18	389	Metastatic	Biopsy-Core	Adenocarcinoma	Prostate	389-B	0	
7/26/18	390	Metastatic	Venipuncture	N/A	CTC	390-1	0	
8/31/18	391	Primary	Radical Prostatectomy	Adenocarcinoma	Prostate	391-12	0	
						391-14	0	
10/12/18	392	Metastatic	Biopsy-Core	Adenocarcinoma	Lymph Node	392-1	0	
11/6/18	393	Metastatic	Venipuncture	N/A	CTC	393-1	0	
11/7/18	394	Metastatic	Paracentesis	N/A	Peritoneal Cavity	394-1	0	

CTC: Circulating tumor cells.

Major Task 2*:* Identify prostate cancer PDX responders and nonresponders (primary resistance) to treatment with specific drugs and establish treatment-resistant PDX lines.

Subtask 2: Identify prostate cancer PDX responders and nonresponders (primary resistance) to cabozantinib and develop cabozantinib-resistant PDX lines (acquired resistance). This subtask was not pursued because two phase III trials, COMET-1 and COMET-2, have reported that cabozantinib did not extend overall survival (OS) outcomes compared to prednisone and prednisone plus mitoxantrone, respectively, in unselected post-docetaxel patients with metastatic castration-resistant prostate cancer.[1]

Subtask 3: Identify prostate cancer PDX responders and nonresponders (primary resistance) to dovitinib and develop dovitinib-resistant PDX lines (acquired resistance) (MD Anderson, Dr. Navone Laboratory).

The impetus for the studies with dovitinib (Novartis Pharma), an FGFR inhibitor, was that dovitinib demonstrated antitumor activity in a clinical study of men with prostate cancer.[2] However, dovitinib was withdrawn from the clinic and a pan-FGFR kinase inhibitor, which is currently in a clinical phase I trial (NVP-BGJ398; Novartis Pharmaceuticals), is the lead compound being tested as anticancer therapy by Novartis. In addition, in an agreement with Janssen Pharmaceutical Companies of Johnson & Johnson we obtained a pan-FGFR inhibitor (JNJS 42756493) to test in a preclinical setting.

We tested the antitumor activity of JNJS 42756493 and NVP-BGJ398 against prostate cancer PDXs growing in bone. For this we used MDA PCa 118b PDX because they were responders in the study conducted using Dovitinib. We found that JNJS 42756493 (but not NVP-BGJ398) had antitumor activity against MDA PCa 118b PDX growing in the bones of mice. The studies using JNJS 42756493 were performed after we received approval from DOD to use it in our studies instead of dovitinib. The reason is because, as we mentioned, dovitinib is no longer available for clinical studies and JNJS 42756493, which is currently used in our department to treat men with bladder cancer, is the FGFR inhibitor with the most potent antitumor activity of the ones we tested.

JNJS 42756493 half-maximal inhibitory concentration values are in the low nanomolar range for all members of the FGFR family (FGFR1 to FGFR4), with minimal activity on vascular endothelial growth factor receptor (VEGFR) kinases compared with FGFR kinases (approximately 20-fold potency difference). We tested JNJS antitumor activity against 2 different prostate cancer PDXs: MDA PCa 118b,

which expresses high levels FGFR1, and MDA PCa 183, which has no detectable FGFR1 expression (**Figure 1**).

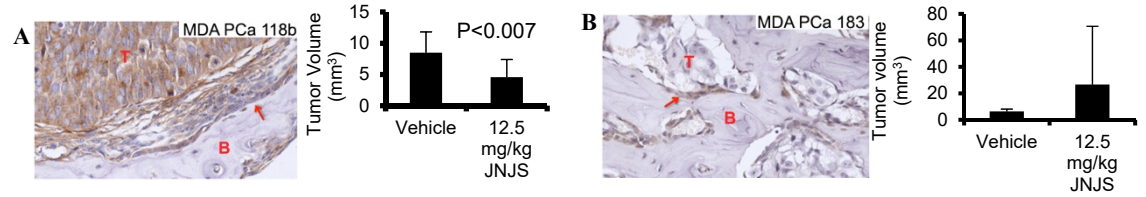

Figure 1. Immunohistochemical analysis of FGFR1 expression in MDA PCa 118b (**A**-left panel) and MDA PCa 183 (**B**-left panel) PDXs growing subcutaneously in SCID mice. Tumor volume measured from serial sagittal MR images of femurs bearing MDA PCa 118b (**A**-right panel) and MDA PCa 183 (**B**-right panel) derived tumors in control and treated mice. T, tumor; B, bone; Arrow, osteoblasts.

***Major Task 3**: Perform integrative genomic analysis of responder as well as primary and secondary treatment-resistant prostate cancer PDXs* (University of Michigan, Dr. Chinnaiyan Laboratory, and MD Anderson, Dr. Navone Laboratory).

Subtask 1: Dr. Arul Chinnaiyan at the University of Michigan assessed expression levels of FGFR1 transcripts by RNA sequencing of 183 human prostate cancer samples and of PDXs. The length of the protein isoforms related to the predicted transcripts, found by RNA sequencing, range between 731 to 853aa. When performing the analysis, we identified eight different protein-coding transcripts to be the most abundantly expressed, (with a predicted protein length of 820 to 853aa); probably reflecting FGFR1 alpha and FGFR1 beta isoforms (**Table 2**). We thus focused our studies on these two best-characterized isoforms. Also, we found that all PDXs tested express primarily FGFR1 alpha isoform while prostate cancer cell lines express FGFR1 beta.

Most abundant expressed transcripts	Predicted protein length
ENST00000326324	731-733 aa
ENST00000356207	
ENST00000397103	
ENST00000397091	820-853 aa
ENST00000397108	
ENST00000397113	
ENST00000425967	
ENST00000532791	

Table 2. Different prostate cancer tissue samples express different FGFR1 isoforms. RNA sequencing analysis of FGFR1 transcripts in human prostate cancer samples and PDXs (performed in collaboration with Dr. Arul Chinnaiyan, MCTP).

In collaboration with Bradley Broom (Professor, Department of Bioinformatics and Computational Biology), we mined the human RNA sequencing data from TCGA for expression of FGFR1 isoforms and their molecular and clinical correlates. The search was performed using the specific sequence of each of the FGFR1 isoforms, alpha and beta. To perform the analyses, an FGFR1 splice score was defined as the ratio between FGFR1 alpha versus FGFR1 beta. A high FGFR1 score indicates prevalence of FGFR1 alpha and a low FGFR1 score indicates prevalence of FGFR1 beta. We subsequently assessed the expression of genes and pathways associated to FGFR1 splice score. **Figure 2** is a heatmap showing the top 2000 genes positively or negatively correlated with the FGFR1 splice score. In **Figure 1**, two patterns of expression are observed, with higher expression of the genes that are negatively correlated (highly correlated with isoform beta) than of those that are positively correlated (highly correlated with

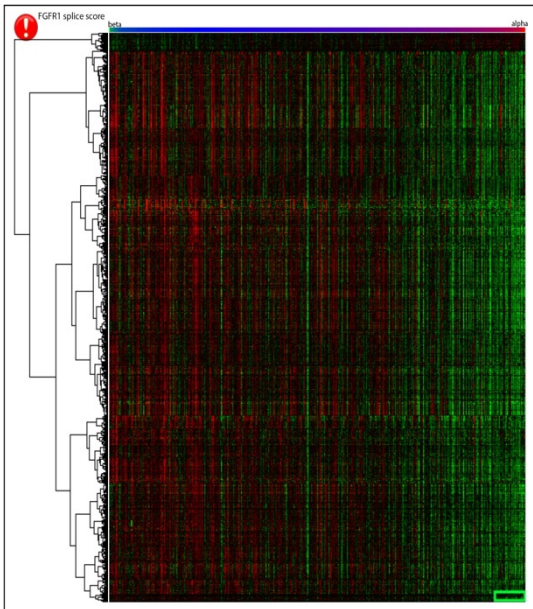

Figure 2. Snapshot of heatmap showing the 2000 most highly correlated genes positively or negatively. Each column represents a sample. Each row represents a gene. Organized according to the expression ratio between alpha and beta (left, low splice score and right, high splice score). Green: negatively correlated genes; Red: positively correlated genes.

isoform alpha) with the FGFR1 splicing score. Then, we evaluated the 20 most correlated genes with FGFR1 splice score. Among the genes with highest correlation to FGFR1 splice score, Calcium-Activated Nucleotidase 1 (CANT1) and UDP-N-Acetylglucosamine Pyrophosphorylase 1 (UAP1) could be of further interest, because they are highly expressed in prostate cancer and are androgen regulated.[3-5] On the other hand, none of the 20 genes most correlated to the beta isoform (lowest correlation) has been previously associated with prostate cancer. Nevertheless, we observe that the fold change in correlation for the group of genes related to alpha is weak (i.e., around 0.3) and for beta, medium (i.e., around 0.5). So, we decided to focus on the pathways associated with FGFR1 splice score.

We then identified pathways correlated with FGFR1 splice score. Since many pathways are associated with FGFR1 splice score with a statistically significant *P* value (particularly true for pathways associated with beta isoform [approximately 750 pathways]), we decided to prioritize those pathways with a *P* value < 0.002 and an observed gene set enrichment score (ES) value falling the farthest from a random distribution (empirical *P* value). Under these criteria we found two alpha-associated pathways, namely mitochondrial tRNA aminoacylation and aminoacyl tRNA biosynthesis with *P* values < 0.002 and = 0.00956, respectively (**Figure 3**).

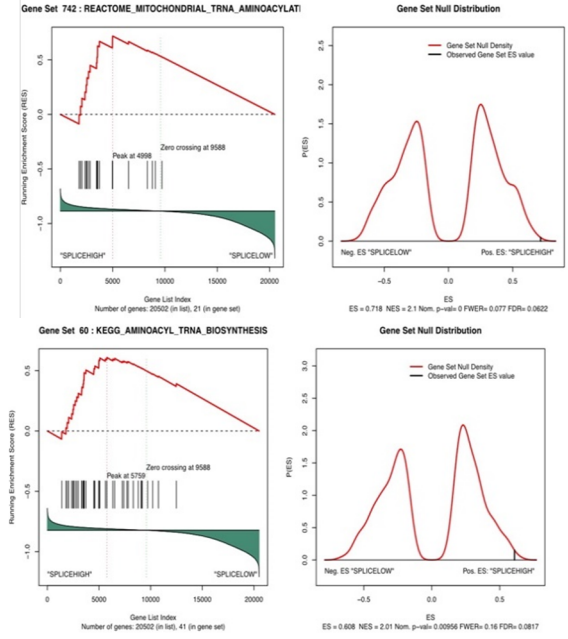

Figure 3. Pathways associated to FGFR1 alpha (SPLICEHIGH) with highest *P* value and empirical *P* value.

At first glance, many of the pathways associated with FGFR1 beta isoform are immune system-related. Using a *P* value < 0.002 and the empirical *P* value criteria, we found that the MAPK signaling cascade, signaling by FGFR in disease, and pathways in cancer are significantly correlated with FGFR1 beta (but not alpha) isoform (i.e., low FGFR1 splice score).

With respect to the clinical correlates of FGFR1 splice score, unfortunately, there are a limited number of cases with the highest or lowest FGFR1 splice score. In these few samples, a correlation between FGFR1 score and recurrence parameters is found. Parameters of recurrence and non-recurrence related to FGFR1 splice score are yet to be analyzed and plotted.

Expression of FGFR1 isoforms alpha and beta in prostate cancer cells results in different molecular outcomes. We developed C4-2B prostate cancer cells stably expressing a bicistronic vector containing FGFR1 isoforms and green fluorescent protein (GFP) (GenScript). Stable lines were developed by batch transfection and selection with gentamicin followed by cell sorting of GFP-positive cells. The same procedure was used for the selection of all three C4-2B sublines (control empty vector [EV], FGFR1 alpha, and FGFR1 beta). Using these cells, we assessed the signaling pathways activated by FGFs. **Figure 4** illustrates

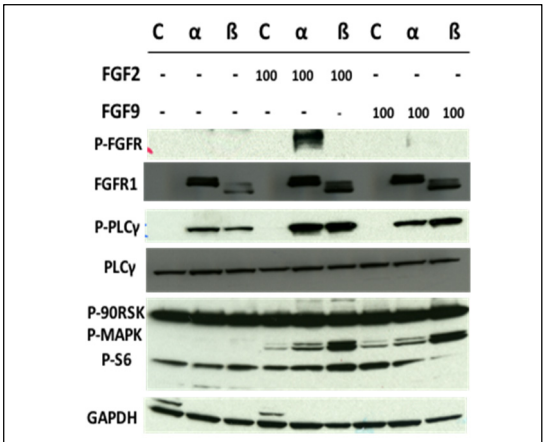

Figure 4. Expression of FGFR1, p-FGFR1, and signaling molecules downstream of FGFR1. C4-2B cells were starved for 3 hrs; Heparan sulfate was added to the medium for 1 hr; then cells were untreated or FGFR1 signaling was induced with FGF2 and FGF9 for 45 minutes; cells were then collected and Western blot analysis was performed. Similar results were obtained in an independent experiment.

our finding that phosphorylation of FGFR1 occurs only in cells expressing the alpha isoform. To detect FGFR1 phosphorylation, we used an antibody that recognizes Tyr653/654. These phosphorylation sites are important for catalytic activity of activated FGFR and are essential for signaling. Nevertheless, seven tyrosine residues in the cytoplasmic tail of FGFR1 can be phosphorylated: Tyr463, 583, 585, 653, 654, 730, and 766. These phosphorylated tyrosine residues may provide docking sites for downstream signaling components such as Crk and PLCγ. On the other hand, we observe significantly higher phosphorylation of MAPK (p42/44) in cells expressing the beta isoform compared to alpha. These results are in agreement with our *in silico* findings that the MAPK cascade is significantly associated with the beta isoform.

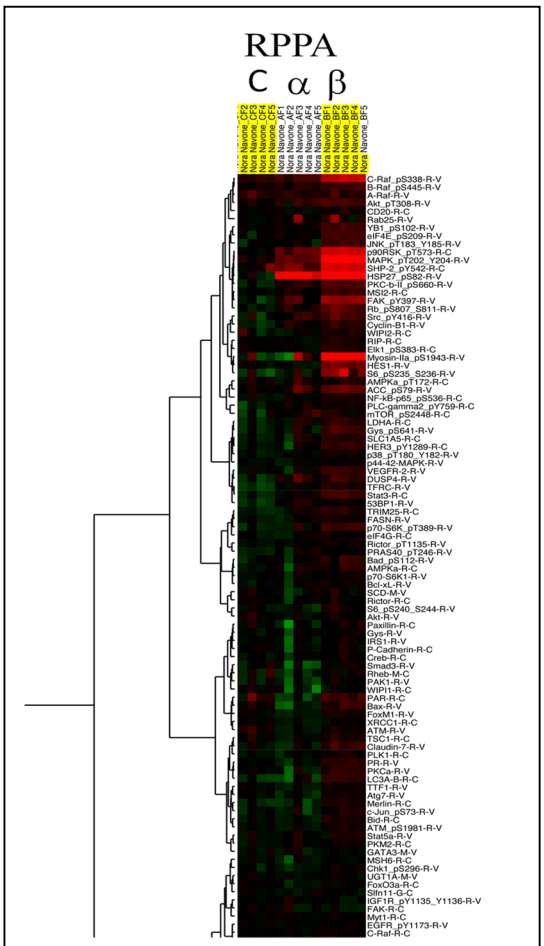

Figure 5. RPPA results of C4-2B cells expressing EV (C) FGFR1 α or β and treated with FGF2.

We have subsequently performed RPPA analysis of PCa C4-2B cells genetically engineered to express FGFR1 isoforms alpha and beta or EV induced with FGF2 (100 ng/mL). The corresponding statistical analysis was performed based on the discussion of results with Dr. Bradley Broom (Dept. Of Bioinformatics and Comp. Biology, MD Anderson). Specifically, an adjusted *P* value, corrected by the number of events, was calculated to eliminate false positives. Again, in agreement with our *in silico* findings, we have detected MAPK phosphorylation significantly associated with the induced beta isoform (**Figure 5**). Among the top RPPA candidates are the oncogene YAP1 (which has a reduced phosphorylation associated with translocation into the cytoplasm followed by degradation[6] in C4-2B FGFR1 isoforms), and the metastasis suppressor gene NDRG1 (which is increased in C4-2B FGFR1 isoforms).

Based on these studies, we hypothesize that FGFR1 alpha and beta confer different phenotypes to prostate cancer cells. This may in part underlie prostate cancer's heterogeneity, progression pattern, and differences in response to FGFR1 inhibitor.

Currently there are no commercially available isoform-specific antibodies that work in clinical samples. To determine the expression levels of FGFR1 isoforms in human samples, we had proposed to use isoform-specific antibodies that we developed in collaboration with Creative Biolabs (Upton, NY). Unfortunately, based on our unsuccessful preliminary experiments, the antibodies lack specificity for immunohistochemical (IHC) assay. Hence, we will assess the expression of FGFR1 isoforms by RNA *in situ* hybridization (ISH) in formalin-fixed paraffin-embedded (FFPE) archived samples. We have designed three probes with Advanced Cell Diagnostics, Inc. (Silicon Valley, CA) to perform the proposed studies: Probe 1 (alpha-specific probe), for the exon-exon junction to detect the alpha-specific exon; Probe 2, for the exon-exon junction to detect the skipping of the alpha-specific exon; and Probe 3, targeting common sequences between FGFR1 alpha and beta (**Figure 6**). Probes 1 and 3 will indicate FGFR1 alpha, and Probes 2 and 3 will indicate the presence for FGFR1 beta. We will approach this study by dual color assay and take the ratio to decide on the expression level of each variant. Of

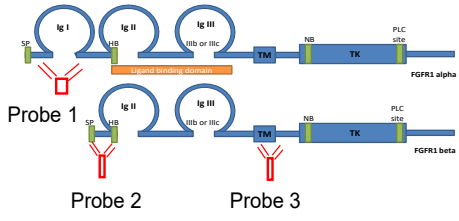

Figure 6. Illustration of probes designed to perform RNA-ISH.

note, multiple FGFR1 splice variants have been reported but FGFR1 alpha and beta are the best characterized. However, although alpha exon is specific for FGFR1 alpha, other FGFR1 variants with alpha-specific exon transcribed could be detected by our strategy (transcript variant 2, 10, 11, 12, and 14), while other variants also have alpha-specific exon skipping (transcript variant 4 and 13). Thus, in this initial phase of our study we will focus on identifying the prevalence of alpha-specific exon-skipping FGFR1 beta versus FGFR1 alpha and some alpha exon-expressing FGFR1 variants. We will subsequently refine our strategy to determine which alpha-specific exon-skipping and alpha exon-expressing FGFR1 variants are detected. The advantage of ISH is that you get information at the cellular level (i.e., intracellular localization of the target molecule can be detected), as well as the distribution within the tissue (and what percentage of cells express the molecule in a sample). These studies are currently ongoing and will be part of a peer-reviewed publication together with all studies outlined in this report.

Survival of mice was significantly reduced after intracardiac injection of prostate cancer cells expressing FGFR1. We subsequently studied whether FGFR1 expression would confer different phenotypes to prostate cancer cells. With that goal, in a pilot study, we injected male SCID mice with PC3 cells stably transfected with FGFR1 alpha and EV. We found that the survival rate of mice intracardially injected with PC3 cells stably transfected with FGFR1 alpha was significantly lower than that of mice injected with PC3 cells stably transfected with EV ($P < 0.0001$) (**Figure 7**). These results suggest that FGFR1 alpha accelerates the aggressive phenotype of prostate cancer cells. Unfortunately, due to the unexpected early death of mice injected with PC3 cells expressing FGFR1 alpha, we did not have enough power to assess whether there was a statistically significant increase in bone metastases. Thus, we repeated this study with two different cell lines, PC3 and C4-2B.

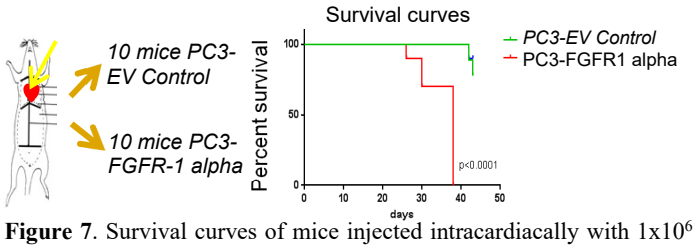

Figure 7. Survival curves of mice injected intracardiacally with $1x10^6$ PC3 cells stably expressing FGFR1 alpha or EV. Statistical analysis Log-rank (Mantel-Cox) test $P<0.0001$.

Metastases were significantly increased after intracardiac injection of prostate cancer cells expressing FGFR1 compared to controls. First, we evaluated the metastatic potential of C4-2B cells expressing luciferase and FGFR1 isoforms (alpha and beta) or EV *in vivo* after intracardiac injection (12 male SCID mice per subline). Since metastases of C4-2B to bone (which are mixed osteoblastic-osteolytic) are not easily identified by X-ray analyses, bone metastases were monitored by quantification of bioluminescence (BLI) using the IVIS imaging system. We further validated the precise location of the areas that showed BLI signal by magnetic resonance imaging (MRI) in collaboration with Dr. Kundra (Dept. of Diagnostic Radiology, MD Anderson) and the Small Animal Imaging Facility. At the end of the study we performed X-ray analyses to determine whether there was a change in the prostate cancer-induced bone reaction.

We found a higher number of overall metastases for the group of mice injected with cells expressing FGFR1 isoforms than EV control; a greater number of mice with metastatic lesions when injecting C4-2B FGFR1 alpha compared to C4-2B EV control and C4-2B FGFR1 beta (**Table 3**). Bone metastases were detected in mice injected with FGFR1 alpha but not in the control EV or FGFR1 beta groups (**Table 3**). Metastatic sites included liver, brain, and mandible. Interestingly, we found that C4-2B cells metastasize to the brain in a high proportion—in particular, C4-2B FGFR1 alpha (25%) compared with C4-2B FGFR1 beta and C4-2B EV control (8%).

Table 3. Metastatic rate of C4-2B cells after intracardiac injection in male SCID mice

	Mice with metastases	Metastases per mouse	Mice with bone metastases
C4-2B EV	1/12 (8%)	1	0/12 (0%)
C4-2B FGFR1 alpha	3/12 (25%)	1-3	1/12 (8%)
C4-2B FGFR1 beta	1/12 (8%)	2	0/12 (0%)

Also, after validating expression of FGFR1 in PC3 cells by IHC and Western blot in the pilot study, we performed a second independent study to assess the metastatic dissemination of PC3-expressing FGFR1 isoforms or EV after intracardiac injection. Since PC3 is osteolytic, we monitored bone metastases as osteolytic lesions by X-ray analyses weekly. At the end of the study, we performed necropsies of the mice to detect visceral metastases. We found a statistically significant increase of mice with bone metastases, assessed by X-ray analysis, in the group injected with PC3 FGFR1 alpha and beta compared to PC3 EV at 4 weeks after injection (**Table 4**). A more pronounced phenotype in the group injected with FGFR1 alpha ($P = 0.00005$) was observed than with FGFR1 beta ($P = 0.02474$), compared to EV. These results need to be confirmed by histopathological analysis of bone and visceral tumors, as well as expression levels and distribution of FGFR1 by IHC. As mentioned above, similar results were observed when performing these studies with C4-2B sublines. *These data suggest that FGFR1 accelerates the metastatic phenotype of prostate cancer cells and that the "penetrance" of this effect might be modulated by FGFR1-specific isoforms and by the genetic background of prostate cancer cells*.

Table 4. Rate of bone metastases after intracardiac injection of PC3 cells

	Mice with bone lesions
PC3 EV	0/12 (0%)
PC3 FGFR1 alpha	11/12 (92%)
PC3 FGFR1 beta	6/12 (50%)

FGFR1 expression by prostate cancer cells does not affect tumor volume after direct intrabone injection. We evaluated tumor growth in bone and the bone reaction of C4-2B cells expressing FGFR1 isoforms (alpha and beta) and EV *in vivo* after direct injection into the right femur of male SCID mice (6 mice per subline). Left legs served as sham-injected non-tumor-bearing controls. We studied the growth of prostate cancer cells in bone by X-ray analyses at different time points and by MRI at the end of the study to assess tumor volume. After the mice were killed, we dissected tumor-bearing bones and studied the specimens by high-resolution microCT and bone histomorphometry of undecalcified bone to assess bone parameters (e.g., bone mass and osteoblast and osteoclast numbers). We also performed immunohistopathology analyses of formalin-fixed paraffin-embedded specimens. At the time of harvest, the femurs were very fragile in all three groups in general. Later, when H&E was performed, we observed tumor all over the femur, which probably accounts for the fragility of the samples.

We found no significant differences in tumor volume by MRI analysis when comparing C4-2B-FGFR1 tumor-bearing femurs compared to C4-2B-EV tumor-bearing femurs. We also found that C4-2B expressing FGFR1 beta showed a decrease in osteoblast (OB) parameters (e.g., number of OB/tissue area of interest; $P < 0.004$) and an increase in osteoclast (OC) parameters (e.g., OC surface/bone surface; $P < 0.036$) compared with C4-2B expressing EV. These results indicate that prostate cancer cells expressing FGFR1 beta activate OCs.

MicroCT analysis of tumor-bearing femurs indicated a decrease in bone volume of the femurs injected with C4-2B expressing FGFR1 beta when compared to C4-2B expressing EV ($P = 0.024$). In part, this could be a result of a decrease in osteoblast number ($P = 0.001$) and osteoblast surface ($P = 0.0005$) as assayed by bone histomorphometry. Two sample *t* tests were used for analyses of the quantitative data, comparing the FGFR1-expressing isoform, either alpha or beta, sample group versus control group.

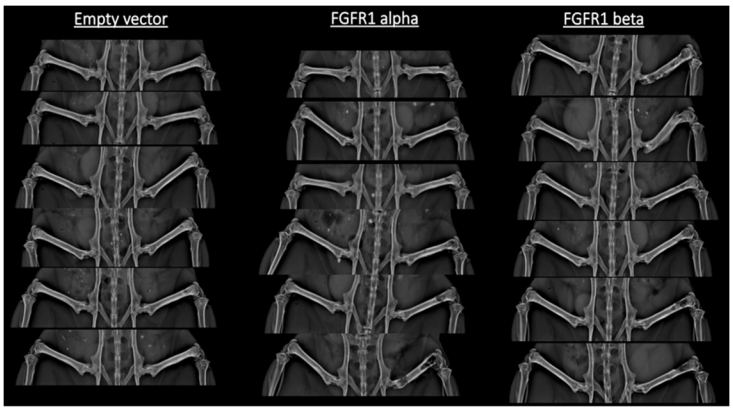

Figure 8. Radiographs of mice hemipelvis and rear limbs at 4 weeks after intrafemoral injection of PC3 cells expressing FGFR1 alpha, beta, or EV. Suspicious osteolytic lesions are illustrated as radiolucent areas.

We have also evaluated tumor growth in

bone and the bone reaction of PC3 cells expressing FGFR1 isoforms (alpha and beta) and EV *in vivo* after direct injection into the right femur of male SCID mice (6 mice per subline). Since PC3 are very osteolytic and grow fast, the number of cells injected was reduced to 50,000. Left legs served as sham-injected non-tumor-bearing controls. We evaluated tumor growth in bone and the bone reaction by X-ray analyses at different time points. After the mice were killed, we dissected tumor-bearing bones. The X-ray images show pronounced osteolytic lesions in the bones injected with PC3-FGFR1 compared to PC3-EV (**Figure 8**).

What opportunities for training and professional development has the project provided?

Estefania Labanca is a Graduate Research Assistant in my laboratory and works on this project. The study of the role of FGFR in prostate cancer is the subject of her studies toward a PhD at GSBS. In the process of carrying forward all aspects of this project she grew scientifically, got an unconditional pass in her candidacy exam, and was selected by the Graduate School of Biomedical Sciences Student Scholarship Committee and the Deans to receive the 2017-2018 Floyd Haar, MD Endowed Memorial Scholarship in Memory of Freda Haar. This award recognizes outstanding GSBS students conducting critical research on cancer.

How were the results disseminated to communities of interest?

Posters at National Conferences

Poster. American Association for Cancer Research Special Conference: Prostate Cancer: Advances in Basic, Translational, and Clinical Research (Orlando, FL, USA, Dec 2-5, 2017) "Expression of fibroblast growth factor 1 isoforms and activation of different pathways in prostate cancer progression." **Labanca E**, Yang J, Shepherd P, Roberts J, Starbuck M, Broom B, Iyer M, Logothetis C, Chinnaiyan A, Navone N. Published in Proc. AACR Special Conference (2017) Abstract A026.

Poster. American Association for Cancer Research Annual Meeting 2016 (New Orleans, LA, USA, April 16-20) "Alpha and beta isoforms of fibroblast growth factor receptor 1 in prostate cancers." **Labanca E**, Wan X, Yang J,Iyer M, Logothetis C, Chinnaiyan A, Navone N. Published in Proc. AACR (2016) Abstract 1871.

Presentations at National or International Conferences. Invited

Navone, NM. The bone microenvironment and its role in prostate cancer progression, Prostate Cancer Foundation (PCF) New York, NY, 9/8/2016

Navone, NM. Targeting the bone compartment in metastatic prostate cancer, Prostate Cancer Foundation (PCF) 23rd Annual Scientific Retreat, Carlsbad, CA, 10/2016

Navone, NM. The pathogenesis of castrate resistant progression of prostate cancer in bone, 61st Annual Scientific Meeting of the Argentine Society for Clinical Investigation (SAIC), Mar del Plata, Mar del Plata, Buenos Aires, Argentina, 11/2016

Navone, NM. Targeting the bone compartment in metastatic prostate cancer, 2nd Fibroblast Growth Factors in Development and Repair Conference, Cancun, Mexico, 3/2017

Navone, NM. Targeting the bone compartment in metastatic prostate cancer, The 2nd Leo and Anne Albert Charitable Trust Workshop: Reducing the Burden of Bone Metastatic Prostate Cancer, La Jolla, CA, 3/2017

Seminar Invitations from Other Institutions

Targeting the bone compartment in metastatic prostate cancer, Pathology Grand Rounds, The University of Alabama at Birmingham, Birmingham, AL, 2017

Targeting the bone compartment in metastatic prostate cancer, The Cancer Research Grand Rounds, Henry Ford Health System, Department of Public Health Sciences, Detroit, MI, 2017

FGFR1 in prostate cancer progression, University of Houston Department of Biology & Biochemistry, Houston, TX, 5/1/2018

What do you plan to do during the next reporting period to accomplish the goals?

Not applicable. This is our final report.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

We have developed unique resources and made novel discoveries as detailed below:

- We have established a series of PDXs that will be made available to the scientific community for research.
- We discovered, for the first time, that FGFR1 isoforms alpha and beta are associated with the expression of different genes. This may in part underlie prostate cancer's heterogeneity and progression pattern.
- We discovered that FGFR1 accelerates prostate cancer metastases in experimental systems.
- We have identified a specific pan-FGFR inhibitor (JNJS 42756493) that has antitumor activity against PDXs expressing high FGFR1.

Together these findings provide support to move forward with a clinical study using JNJS 42756493 in men with advanced prostate cancer.

What was the impact on other disciplines?

Nothing to report

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

N/A, Final report

Actual or anticipated problems or delays and actions or plans to resolve them

Changes that had a significant impact on expenditures

N/A, Final report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

N/A, Final report

Significant changes in use or care of human subjects

N/A, Final report

Significant changes in use or care of vertebrate animals

N/A, Final report

Significant changes in use of biohazards and/or select agents

N/A, Final report

6. PRODUCTS

Publications, conference papers, and presentations

Posters at national conferences

Poster. American Association for Cancer Research Special Conference: Prostate Cancer: Advances in Basic, Translational, and Clinical Research (Orlando, FL, USA, Dec 2-5, 2017) "Expression of fibroblast growth factor 1 isoforms and activation of different pathways in prostate cancer progression." **Labanca E**, Yang J, Shepherd P, Roberts J, Starbuck M, Broom B, Iyer M, Logothetis C, Chinnaiyan A, Navone N. Published in Proc. AACR Special Conference (2017) Abstract A026.

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Targeting the bone compartment in metastatic prostate cancer, The Cancer Research Grand Rounds, Henry Ford Health System, Department of Public Health Sciences, Detroit, MI, 2017

FGFR1 in prostate cancer progression, University of Houston Department of Biology & Biochemistry, Houston, TX, 5/1/2018

Journal publications

Nothing to report

Books or other non-periodical, one-time publications

Nothing to report

Other publications, conference papers and presentations

Nothing to report

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other products

Development of PDXs that will be made available to the scientific community.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

The following individuals participated in this project:

The University of Texas MD Anderson Cancer Center

Name:	**Nora M. Navone**
Project Role:	Principal Investigator
Nearest person month worked:	1.80 calendar months (Years 1-3 and NCE)

Contribution to Project:	Dr. Navone was responsible for designing the experiments, evaluating the results, coordinating the personnel's efforts related to all *in vivo* studies in mice, and preparing prostate cancer cells derived from human prostate cancer xenografts. She interacted with Dr. Chinnaiyan to integrate the research efforts within this project.
Funding Support:	Funding support was provided from this award.
Name:	**John Araujo**
Project Role:	Co-Principal Investigator
Nearest person month worked:	0.12 calendar months (Years 1-3 and NCE)
Contribution to Project:	Dr. Araujo provided clinical data on the follow-up of men whose prostate cancer was the source of prostate cancer xenografts or was a tissue specimen used for genomic analysis. He worked closely with Dr. Navone in the analysis of these data and their correlation with molecular studies.
Funding Support:	Funding support was provided from this award.

Name:	**Bradley Broom**
Project Role:	Collaborator
Nearest person month worked:	0.24 calendar months (Years 1-3 and NCE)
Contribution to Project:	Dr. Broom provided expertise in biostatistics to analyze the data emerging from the preclinical studies, including the molecular studies, and relate them to the findings emerging from the clinic.
Funding Support:	Funding support was provided from this award.

Name:	**Xinhai Wan**
Project Role:	Collaborator
Nearest person month worked:	4.80 calendar months (Years 1-2 up to 7/31/2016)
Contribution to Project:	Dr. Wan was responsible for intrabone injection of prostate cancer cells in mice and the *in vivo* experiments involving laboratory animals. He did the immunohistochemical studies of tissue samples and the molecular and cell biology studies related to the *in vivo* studies. He communicated with oncologists and pathologists to collect the information and discuss the interpretation of the results.
Funding Support:	Funding support was provided from this award.

Name:	**Estefania Labanca**
Project Role:	Graduate Research Assistant-GSBS
Nearest person month worked:	3.60 calendar months (Year 2), 6.0 calendar months (Year 3 and NCE)
Contribution to Project:	Upon *Xinhai Wan's* departure from the department on 7/31/2016, Ms. Labanca was responsible for intrabone injection of prostate cancer cells in mice and the *in vivo* experiments involving laboratory animals. She performed the immunohistochemical studies of tissue samples and the molecular and cell biology studies related to the *in vivo* studies. Dr. Wan trained her in these techniques before he left.
Funding Support:	Salary support was provided from this grant.

Name:	**Jun Yang**
Project Role:	Research Laboratory Coordinator
Nearest person month worked:	3 calendar months (Years 1-2), 4.80 calendar months (Year 3 and NCE)

Contribution to Project:	Ms. Yang prepared cell and tumor lines for the planned experiments and performed assays involving molecular and cell biology techniques. She also provided technical support for the experiments involving *in vivo* manipulation of animals and ordered supplies.
Funding Support:	Funding support was provided from this award.

The University of Michigan

Name:	**Arul Chinnaiyan**
Project Role:	Partnering PI
Nearest person month worked:	0.60 calendar months (Years 1-3 and NCE)
Contribution to Project:	Dr. Chinnaiyan was responsible for overall oversight of the project and co-directed the CLIA-certified lab. He made sure the project produced high-quality data and coordinated the efforts of the personnel and collaborators. He closely interacted with Dr. Navone to integrate the research efforts within this project.
Funding Support:	He received salary from the Howard Hughes Medical Institute

Name:	**Dan Robinson**
Project Role:	Co-Investigator
Nearest person month worked:	1.92 calendar months (Years 1-3); 0.60 calendar months (NCE)
Contribution to Project:	Oversaw the preparation of sequencing libraries and provided quality control and expertise in genome biology.
Funding Support:	Funding support was provided from this award

Name:	**Yi-Mi Wu**
Project Role:	Co-Investigator
Nearest person month worked:	3.60 calendar months (Years 1-3)
Contribution to Project:	Guided the project's research development and facilitated interpretation of sequence data.
Funding Support:	Funding support was provided from this award

Name:	**Xiaoxuan Dang**
Project Role:	Sequencing Technician
Nearest person month worked:	6.0 calendar months (Year 1), 3.0 calendar months (Years 2-3), 0.75 calendar months (NCE)
Contribution to Project:	Assisted in library generation and sequencing.
Funding Support:	Funding support was provided from this award

Name:	**Robert Lonigro**
Project Role:	Bioinformatics Analyst
Nearest person month worked:	1.20 calendar months (Year 1), 2.40 calendar months (Year 2), 0.60 calendar months (Year 3)
Contribution to Project:	Provided bioinformatic analysis in the context of candidate gene nominations.
Funding Support:	Funding support was provided from this award

Name:	**Jean Tien**
Project Role:	Research Investigator
Nearest person month worked:	2.40 calendar months (Year 2)
Contribution to Project:	PDX models
Funding Support:	Funding support was provided from this award

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Yes, the active other support for key personnel has changed. Several grants have expired and new ones have been awarded. We are including the updated active other support below for key personnel.

MD ANDERSON KEY PERSONNEL

NAVONE, Nora
CURRENT

2013-0933 **(Araujo)**
Title: **An Observation, Open Label Study of Alpharadin (Radium 223) in Patients with Castrate Resistant Prostate Cancer Bone Metastases**
Time Commitments: 0.0 calendar
Supporting Agency: Bayer
Performance Period: 07/02/2014-12/31/2018
Level of Funding:
Goals: This is an open-label study to determine the effect of alpharadin on the bone marrow microenvironment in patients with castrate-resistant prostate cancer (CRPC) and bone metastases. We will determine the modulation of bone microenvironment as measured by serum, plasma, urine, and bone marrow aspirate bone markers.
Specific Aims: The primary objective is to identify markers of both predictive and prognostic importance within bone marrow biopsies, aspirates as well as serum in patients with metastatic CRPC to bone, to be treated with the standard 6 doses of alpharadin. The secondary objectives are:
1) Link prostate specimen antigen initial concentration to modulation of bone markers, in the blood, urine, and bone marrow plasma of study patients. 2) Estimate the efficacy and progression free survival by PCWG2 in study patients. 3) Develop a deeply annotated tissue repository for later hypothesis-generating associations. 4) Estimate the overall survival in patients with CRPC.
Role: Co-Investigator

Janssen **(Navone)**
Title: **FGFR Inhibitors in Prostate Cancer Bone Metastasis**
Time Commitments: 1.80 calendar
Supporting Agency: Janssen Research and Development
Grants Officer Address: James Bischoff, Sr. Director, Phone: 215-628-5971, jbischol@its.jnj.com
Jhilik De, Administrative Contact, Jde5@its.jnj.com
Performance Period: 08/14/2014-07/31/2019
Level of Funding:

Goals:	This program's goal is to test the antitumor efficacy of a pan-FGFR inhibitor against patient-derived xenografts developed in my laboratory.
Specific Aims:	1) Assess the efficacy of pan-FGFR inhibitor(s) (company material) on prostate cancer PDXs growing in the bones of male SCID mice. 2) Assess the efficacy of company material on the growth of prostate cancer PDXs in bones of male SCID mice. 3) Screen tissue microarrays (TMAs) containing prostate cancer PDXs for expression of targets of interest to company.
Role:	Principal Investigator

P50 CA140388-08	**(Logothetis)**
Title:	**Developmental Research Program Award: Fibroblast Growth Factor Receptor 1 and its Isoforms in Prostate Cancer Progression to Metastases**
Time Commitments:	1.20 calendar
Supporting Agency:	NIH/NCI/MD Anderson
Grants Officer Address:	Carrie C. Feighl, Director, Research Finance, 713-792-3477, cfeighl@mdanderson.org
Performance Period:	09/01/2018-08/31/2019
Level of Funding:	$50,000 direct
Goals/Aims:	1) To examine the signaling cascade induced by FGFR1 isoforms and to identify the gene signature associated with FGFR1-mediated metastases. 2) To study FGFR1 isoform expression and its clinical and molecular correlates in human prostate cancer tissue specimens.
Role:	PI, Developmental Research Program Award

P50 CA140388-08	**(Logothetis-PI, Weigel-DRP PI)**
Title:	**Developmental Research Program Award: Can Androgen Receptor (AR) Isoform-Specific Changes in Gene Expression and Cell Signaling Pathways Serve as Markers of Variant Activity and Candidate Therapeutic Targets?**
Time Commitments:	0 calendar
Supporting Agency:	NIH/NCI/MD Anderson
Grants Officer Address:	Carrie C. Feighl, Director, Research Finance, 713-792-3477, cfeighl@mdanderson.org
Performance Period:	09/01/2018-08/31/2019
Level of Funding:	
Goals/Aims:	We seek to develop a gene signature based on the genes regulated by the constitutively active androgen receptor splice variant AR-V7 that will allow us to determine whether a patient who has failed first-line androgen deprivation therapy will exhibit *de novo* resistance to abiraterone or enzalutamide. We also seek to confirm the activation of lipid signaling and YAP/tAZ in our current models, extend analyses of additional models and begin preliminary tests of functional relevance.
Role:	MDA Collaborator, Developmental Research Program Award

17CHAL12	**(Jones)**
Title:	**Molecular Risk Stratification of Prostate Cancer in African American U.S. Veterans**

	Parent Grant Title: Clinicopathological Correlation & Molecular Signature Identification & Risk Stratification of Prostate Cancer in African American U.S. Veterans, With & Without Exposure to Battlefield Chemicals
Time Commitments:	0.60 calendar
Supporting Agency:	PCF-Baylor College of Medicine
Grants Officer Address:	Baylor College of Medicine
Performance Period:	12/31/2017-12/31/2019
Level of Funding:	
Goals:	Isolate circulating tumor cells (CTCs) from the blood of African American and Caucasian men with prostate cancer. CTCs will be used at Baylor to perform RNA sequencing, and we will use CTCs to develop PDXs. PDXs will also be used to study the role of AR in racial disparity.
Specific Aims:	Same as above
Role:	Subcontract Principal Investigator

R01 CA193362	**(Yang)**
Title:	**Role of Integrin VLA-6 in Suppression of Bone Formation in Myeloma**
Time Commitments:	0.60 calendar
Supporting Agency:	NIH/NCI
Grants Officer Address:	LeSchell D. Browne, Phone: 240-276-5432, leschell.browne@nih.gov
Performance Period:	02/01/2016-01/31/2021
Level of Funding:	
Goals:	The goal of this project is to investigate the mechanism by which myeloma cells alter the balance of adipogenesis and osteoblastogenesis, thereby suppressing bone formation.
Specific Aims:	1) Determine whether the α6 integrin in myeloma cells enhances adipogenesis and suppresses osteoblastogenesis and bone formation. 2) Determine whether α6 in myeloma cells binds to its ligand in MSCs to activate a signaling pathway(s) that enhances adipocyte and inhibits osteoblast differentiation.
Role:	Co-Investigator

2 P50 CA140388-08	**(Logothetis/Thompson)**
Title:	**MD Anderson Cancer Center Prostate Cancer SPORE** **Core 2: Biospecimen and Pathology Core**
Time Commitments:	0.60 calendar
Supporting Agency:	NIH/NCI
Grants Officer Address:	Martinson Owusu, Phone: 240-276-6297, owusumo@mail.nih.gov
Performance Period:	09/01/2016-08/31/2021
Level of Funding:	
Goals:	The goal of this Core is to provide the infrastructure, biorepository, xenograft facility, pathological and technical expertise, and informatic infrastructure required to support the projects of the MD Anderson Prostate Cancer SPORE and ensure the achievement of their goals.
Specific Aims:	1) Collect, process, annotate, characterize, store, and distribute human bio-specimens related to prostate cancer. 2) Create well-characterized and quality-controlled tissue derivatives (including PDXs) for translational research and conduct selected tissue-based studies. 3) Provide investigators

with expertise to optimally select and use biospecimen resources, analytical techniques, and interpretation of tissue-based studies. 4) Provide an informatics solution that tightly integrates biospecimen acquisition, annotation, and analysis workflows with clinical data in a secure and accessible manner.

Role: Co-Investigator, Core 2

OVERLAP: None

ARAUJO, John

CURRENT

2013-0933 **(Araujo)**

Title: **An Observation, Open Label Study of Alpharadin (Radium 223) in Patients with Castrate Resistant Prostate Cancer Bone Metastases (NCT02135484)**

Time Commitment: 0 calendar
Supporting Agency: Bayer Healthcare
Performance Period: 07/02/2014-12/31/2018
Level of Funding:
Project Goals/Aims: The goal of this clinical research study is to learn more about how the study drug alpharadin (Radium-223) works in patients who have CPRC that has spread to the bone.
Role: Principal Investigator

VMT-VT-464-CL-001 **(Araujo)**

Title: **A Phase I/II Open-Label, Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of VT-464 in Chemotherapy-Naive Patients with Castration-Refractory Prostate Cancer**

Time Commitment: 0.12 calendar
Supporting Agency: Viamet Pharmaceuticals
Grant Officer Address: 4505 Emperor Boulevard, Suite 300, Durham, NC 27703
Performance Period: 06/12/2012-06/11/2019
Level of Funding:
Project Goals/Aims: The goal is to conduct a phase I/II clinical research study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of VT-464 in chemotherapy in patients with castration-refractory prostate cancer.
Role: Principal Investigator

2015-1134 **(Nabell)**

Title: **A Phase 2 Trial using Gilotrif for Advanced Penile Squamous Cell Carcinoma Following Systemic Therapy**

Time Commitment: 0 calendar
Supporting Agency: Boehringer Ingelheim Pharm/University of Alabama - Birmingham
Performance Period: 12/07/2016-12/06/2019
Level of Funding:
Project Goals/Aims: The goal of this clinical research study is to evaluate the drug Gilotrif in patients with metastatic progressive PSCC following chemotherapy.
Role: MDA Chairman

2014-0026	**(Araujo)**
Title:	**A Phase 2 Study of Oral Selinexor (KPT-330) in Metastatic Castrate Resistant Prostate Adenocarcinoma**
Time Commitment:	0 calendar
Supporting Agency:	Karyopharm Therapeutics
Grant Officer Address:	85 Wells Ave., 2nd Floor, Newton, MA 02459
Performance Period:	03/14/2014-06/30/2020
Level of Funding:	
Project Goals:	Our objective is to conduct a phase 2 study of oral selinexor (kpt-330) in metastatic castrate-resistant prostate adenocarcinoma.
Specific Aims:	Not applicable
Role:	Principal Investigator

2 P50 CA140388-08	**(Logothetis/Thompson)**
Title:	**MD Anderson Cancer Center Prostate Cancer SPORE. Project 2: Targeting Tumor Microenvironment-induced Therapy Resistance in Prostate Cancer Bone Metastasis**
Time Commitment:	0.60 calendar
Supporting Agency:	NIH/NCI
Grants Officer:	Leslie Hickman, Phone: 301-631-3009, hickmanl@mail.nih.gov
Performance Period:	09/01/2016-08/31/2021
Level of Funding:	
Project Goals:	Our objectives are to develop strategies that can block osteocrine-mediated therapy resistance to enhance treatment efficacy.
Specific Aims:	1) Examine the ability of osteocrines to confer therapy resistance through activation of FAK. 2) Examine the effects of second-generation FAK inhibitors (VS-6063 or VS-4718) on overcoming osteocrine-induced therapy resistance in xenograft mouse models. 3) Conduct a clinical trial to examine the toxicity and efficacy of a FAK inhibitor (VS-6063 or VS-4718) in men with treatment-refractory bone-metastatic castrate-resistant prostate cancer.
Role:	Clinical Co-Leader, Project 2

OVERLAP: None

BROOM, Bradley

CURRENT

5 P30 CA016672	**(Pisters)**
Title:	**Cancer Center Support (CORE) Grant: Bioinformatics Shared Resource (PP-SR22)**
Time Commitment:	1.60 calendar
Supporting Agency:	NIH/NCI
Grants Officer:	Martinson Owusu, Grants Management Specialist Phone: 240-276-6297, owusumo@mail.nih.gov
Performance Period:	07/01/2003-06/30/2019 NCE
Level of Funding:	

Project Goals/Aims: The goal of this shared resource is to assist researchers in the application of state-of-the-art methodology for the development, conduct, and analysis of studies using high-throughput technologies.
Role: Co-Investigator

Bioinformatics Gift **(Weinstein)**
Title: **MD Anderson Cancer Center Bioinformatics Gift**
Time Commitment: 1.80 calendar
Supporting Agency: Michael and Susan Dell Foundation
Grants Officer: Aliya Hussaini
P.O. Box 163867
Austin, TX 78716
Performance Period: 04/24/2011-10/04/2019
Level of Funding:
Project Goals/Aims: The goal of the project is to develop methods of analysis for microarray and sequencing-based data that aid in the development of personalized therapies for cancer on the basis of molecular biomarkers and biosignatures. The projects under way are largely, but not exclusively focused on non-small cell lung cancer.
Role: Co-Investigator

R21 CA223527 **(Thompson/Davis)**
Title: **Lipidomics-based Biomarkers for Risk of Progression in Early Prostate Cancer**
Time Commitment: 0.21 calendar
Supporting Agency: NIH/NCI
Grants Officer: Martinson Owusu, Phone: 240-276-6297, owusumo@mail.nih.gov
Performance Period: 01/01/2018-12/31/2019
Level of Funding:
Project Goals: The overall goal of this project is to conduct experiments to elucidate lipoprotein-driven metabolic pathways and to develop lipidomics-based biomarkers for risk of progression in early prostate cancer.
Specific Aims: 1) Analyze lipid metabolites and lipid signaling in prostate cancer cell lines following genetic induction and depletion of Cav-1. 2) Detect differentially expressed plasma lipidomics signatures from men with indolent versus aggressive prostate cancer.
Role: Co-Investigator

U24 CA199461 **(Weinstein/Broom)**
Title: **"Next Generation" Clustered Heat Maps for Fluent, Interactive Exploration of Omic Data**
Time Commitment: 3.81 calendar
Supporting Agency: NIH/NCI
Grants Officer: Martinson Owusu, Phone: 240-276-6297, owusumo@mail.nih.gov
Performance Period: 09/01/2015-08/31/2020
Level of Funding:
Project Goals: To mature NG-CHM technology for fluent use and sharing by biologists and clinical researchers who are not specialists in informatics and thus

provide a major resource for continued progress in precision, individualized medicine for the benefit of patients and their families.

Specific Aims: 1) Expand and enhance the capabilities of the NG-CHM system. 2) Extend and enhance the graphical NG-CHM builder. 3) Improve the interoperability of the NG-CHM system and integrate further with other tools, frameworks, and systems. 4) Establish an open API database for integrating independent, web-enabled tools. 5) Create additional/expanded compendia of cancer-related public datasets. 6) Actively promote the NG-CHM system and interact with its user community.

Role: Principal Investigator

P50 CA140388-08 **(Logothetis/Thompson)**
Title: **MD Anderson Cancer Center Prostate Cancer SPORE**
Core 1: Biostatistics and Bioinformatics

Time Commitment: 1.44 calendar
Supporting Agency: NIH/NCI
Grants Officer: Martinson Owusu, Phone: 240-276-6297, owusumo@mail.nih.gov
Performance Period: 09/01/2016-08/31/2021
Level of Funding:
Project Goals: To provide comprehensive biostatistic and bioinformatic expertise to ensure statistical integrity and optimize data analysis for the studies in the Prostate SPORE.

Specific Aims: 1) Provide guidance in the design and conduct of clinical trials and other experiments (including high-dimensional genomic and proteomic studies) that arise from the ongoing research of the SPORE. 2) Provide innovative and tailored statistical modeling, simulation techniques, and data analyses as needed for the main projects, developmental research and career development projects, and other cores to achieve their specific aims. 3) Ensure that the results of all projects are based on well-designed experiments and are appropriately interpreted. 4) Provide guidance in the design and use of an information system to store appropriate data generated by all projects; develop integrated computational libraries and tools for producing documented, reproducible statistical and bioinformatics analyses; and support the use of these tools for analyses conducted by and on behalf of the projects.

Role: Co-Director

U24 CA210949 **(Weinstein/Akbani/Mills)**
Title: **Batch Effects in Molecular Profiling Data on Cancers: Detection, Quantitation, Interpretation, and Correction**

Time Commitment: 0.43 calendar
Supporting Agency: NIH/NCI
Grants Officer: Aubrey Bell, Grants Management Specialist, Phone: 240-276-7127
Performance Period: 09/13/2016-08/31/2021
Level of Funding:
Project Goals: The primary goal is to analyze cancer proteomics data for batch effects for various projects specified by the NCI. The data will be checked for batch effects, which will be quantified and the data corrected if needed. A

	secondary goal is to further enhance the batch effects analysis with new algorithms and better quality control algorithms.
Specific Aims:	1) Use our MBatch pipeline to detect, quantitate, interpret, and (when appropriate) correct, batch effects in multiple data types from Center for Cancer Genomics projects (directly responsive to RFA Objective 2). 2) Enhance the MBatch pipeline and website (directly responsive to RFA GDAC Objective 1). 3) Make the MBatch pipeline and tools user friendly, visually interactive, automated, and available for users in the biomedical research community (directly responsive to RFA GDAC Objective 1).
Role:	Co-Investigator

U24 CA210950	**(Akbani/Weinstein/Mills)**
Title:	**Integrated Analysis of Protein Expression Data from the Reverse Phase Protein Array (RPPA) Platform**
Time Commitment:	0.42 calendar
Supporting Agency:	NIH/NCI
Grants Officer:	LeSchell D. Browne, leschell.browne@samhsa.hhs.gov
Performance Period:	09/13/2016-08/31/2021
Level of Funding:	
Project Goals:	To analyze cancer proteomics data from the RPPA platform for various projects specified by the NCI. The proteomics data will be correlated with other data types (RNA, DNA, clinical etc.). A secondary goal is to further enhance the proteomics analysis with new algorithms and better quality control algorithms.
Specific Aims:	1) Extract high-quality, analysis-ready protein expression measures from the RPPA data generated by the Genome Characterization Centers (GCCs) using innovative bioinformatic tools and methodologies in our existing RPPA data analysis pipeline. 2) Conduct integrated analysis of RPPA data and correlate them with clinical and other molecular data. 3) Pathway analysis of RPPA data to identify proteomic pathways that have been substantially altered in the case set of each CCG project. 4) Continue to develop innovative bioinformatic and computational tools and methodologies to improve our RPPA data analysis pipeline.
Role:	Co-Investigator

U01 CA235510	**(Akbani/Broom/Weinstein)**
Title:	**Computational Tools for Analysis and Visualization of Quality Control Issues in Metabolomic Data**
Time Commitment:	1.80 calendar
Supporting Agency:	NIH/NCI
Grants Officer:	Aubrey Bell, Grants Management Specialist, Phone: 240-276-7127
Performance Period:	09/01/2018-08/31/2022
Level of Funding:	
Goals:	Develop software tools to assess and (when appropriate) correct quality control issues in metabolomic data.
Specific Aims:	1) Develop the MetaBatch program for detection, quantitation, diagnosis, interpretation, and (when appropriate) correction of batch and trend effects in metabolomic data. 2) Develop and incorporate new metabolomics-specific algorithms for diagnosis and correction of batch and/or trend

effects. 3) Make the MetaBatch pipeline available to users in the biomedical research community as open-source software on GitHub. 4) Provide plug-in capability and interoperability features for integration of MetaBatch with other tools and environments built by members of the Common Fund Metabolomics Consortium. 5) Actively promote MetaBatch through documentation, training videos, webinars, workshops, and opportunities for user feedback.

Role: Principal Investigator

OVERLAP: None

UNIVERSITY OF MICHIGAN KEY PERSONNEL

CHINNAIYAN, Arul M.

CURRENT

R35CA231996 **(Chinnaiyan)**
Title: **Exploring Precision Oncology: From Gene Fusions to lncRNAs**
Time Commitment: 50% effort, 6.0 calendar
Supporting Agency: NIH
Grants Officer: Tawnya McKee, Program Official, mckeeta@mail.nih.gov
Performance Period: 09/01/18 – 08/31/25
Level of Funding:
Project Goals: To advance the field of precision oncology by providing new community resources, identifying novel biomarkers, exploring the therapeutic targeting of nominated molecular players, and adding to the knowledge-base of cancer development mechanisms, particularly those of lncRNAs.
Specific Aims: N/A
Role: Principal Investigator

R01 CA200660 **(Grembecka, Chinnaiyan)**
Title: **Targeting the MLL complex in Castration Resistant Prostate Cancer**
Time Commitment: 4% effort, 4.8 calendar
Supporting Agency: NIH
Grants Officer: Elesinmogun, Funmi, elesinmf@mail.nih.gov
Performance Period: 08/01/2016-07/31/2021
Level of Funding:
Project Goals: To develop new therapy for castration-resistant prostate cancer patients by blocking the menin-MLL interaction.
Specific Aims: 1) Develop highly potent small molecule inhibitors of the menin-MLL interaction with significantly improved potency in prostate cancer models and optimal *in vivo* properties. 2) We propose to study the mechanism of pharmacologic inhibition of the MLL complex in prostate cancer cells. 3) We will assess the *in vivo* efficacy of the menin-MLL inhibitors in mouse models of prostate cancer and investigate the mechanism of resistance of response to these compounds in prostate cancer models. Upon successful completion of this project we expect to identify promising candidate compound(s) that could be further developed for clinical use to treat metastatic CRPC.
Role: Principal Investigator

U01 CA214170 **(Chinnaiyan)**

Title: **The Early Detection Research Network: Biomarker Development Laboratories (U01):** ***Discovery and qualification of transcriptomic biomarkers for the early detection of aggressive prostate cancer***

Time Commitment: 15% effort, 1.80 calendar
Supporting Agency: NIH/NCI
Grants Officer: Peter Wirth, pw2q@nih.gov
Performance Period: 09/15/2016-08/31/2021
Level of Funding:
Project Goals/Aims: 1) Identify and develop assays to study novel aggressive prostate cancer-associated transcriptomic alterations from our MiTranscriptome analysis. 2) Characterize transcripts from Aim 1 as tissue-based aggressive prostate cancer biomarkers using individual *in situ* hybridization assays and a multiplexed next generation sequencing (NGS). 3) Characterize transcripts from Aim 1 as non-invasive, urine-based aggressive prostate cancer early detection biomarkers through collaboration with our industry partner and multiplexed NGS.
Role: Principal Investigator

U24 CA210967 **(Nesvishkii and Chinnaiyan)**

Title: **University of Michigan Proteogenomics Data Analysis Center**

Time Commitment: 5% effort, 0.6 calendar
Supporting Agency: NIH
Grants Officer: Rodriguez, Henry, rodriguezh@mail.nih.gov
Performance Period: 09/15/2016-08/31/2021
Level of Funding:
Project Goals: To perform integrative analysis of data generated using the Clinical Proteomic Tumor Analysis Consortium (CPTAC). The proposed Center at the University of Michigan will be one of the four Centers funded by CPTAC. It will work, in coordination with other Centers, to analyze and integrate proteomics, genomics, and transcriptomics data generated for 3-4 cancer patient cohorts, ~ 100 samples in each cohort. The Center will generate data analysis reports to be shared with other members of the Consortium.
Specific Aims: 1) Assemble a comprehensive proteogenomics data analysis pipeline enabling application of two complementary strategies: (a) using mass spectrometry-based (MS) proteomics data for protein-level "validation" (and thus prioritization) of novel and aberrant cancer-specific transcripts (including alternative splice forms, mutations, etc.) identified from genomics and transcriptomic data. 2) Apply our computational pipelines to CPTAC-wide data, with a focus on presenting the results to the cancer research community in an easily accessible, highly visual form. 3) UM-PGDAC will engage, in coordination with other CPTAC centers, in a second round of prioritization work to select candidate cancer-specific proteins and peptides for subsequent targeted validation using multiplex proteomic assays.
Role: Principal Investigator

P50 CA186786	**(Chinnaiyan)**
Title:	**SPORE in Prostate Cancer** Project 1: A Precision Medicine Approach to Elucidate Mechanisms of Progression and Resistance to Therapy in Advanced Prostate Cancer. Project 4: Development of IncRnas as Prostate Cancer Biomarkers in Urine Core 3: Tissue Core
Time Commitment:	20% effort, 2.40 calendar
Supporting Agency:	NIH/NCI
Grants Officer:	Andrew Hruszkewycz, Phone: 301-496-8528, hruszkea@mail.nih.gov
Performance Period:	09/11/2014-08/31/2019
Level of Funding:	
Project Goals:	The overall goal of this grant is the development of new approaches to the prevention, early detection, diagnosis, and treatment of prostate cancer through translational research.
Specific Aims:	*Project 1 Aims:* 1) Discovery and nomination of novel molecular subtypes of prostate cancer; 2) Characterize associations of molecular subtypes of prostate cancer with clinical outcome and/or aggressiveness of disease in a radical prostatectomy cohort; 3) Characterize associations of molecular subtypes of prostate cancer with clinical outcome. *Project 4 Aims:* 1) Employ a compendium of prostate cancer RNA-Seq data to nominate IncRNAs for assessment in urine. 2) Develop a urine multiplex panel of IncRNAs (including PCAS and Schalpl) that, when combined with TMPRSS2-ERG, will identify men who are more likely to have prostate cancer and ultimately to prevent unnecessary prostate biopsies in men with a low likelihood of cancer. 3) Define a panel of IncRNAs in urine for the detection of high-grade prostate cancer. In this Aim, we will identify individual IncRNAs or combinations with PGAS+TMPRSS2-ERG that assist in noninvasively detecting high-grade prostate cancer in urine. *Core 3 Aims:* 1) Protect patient welfare; 2) Acquisition and processing of prostate tissues for research; 3) Maintenance of clinical and pathology data with links to molecular studies; 4) Provide high quality pathologic review of prostate tissues; 5) Provide expert pathology consultation; 6) Perform quality assessment of prostate tissues and clinical data; 7) Develop technology appropriate for pathology-based translational research.
Roles:	Overall Program Director, Co-Leader of Projects 1 and 4; Director of Core 1 (Administration) and Co-Core Director of Core 3 (Tissue Core)

OVERLAP: None

ROBINSON, Dan
CURRENT

P50 CA186786	**(Chinnaiyan)**
Title:	**SPORE in Prostate Cancer, Project 1: A Precision Medicine Approach to Elucidate Mechanisms of Progression and Resistance to Therapy in Advanced Prostate Cancer**
Time Commitment:	10% effort, 1.2 calendar

Supporting Agency: NIH/NCI
Grants Officer: Andrew Hruszkewycz, Phone: 301-496-8528, hruszkea@mail.nih.gov
Performance Period: 09/11/2014-08/31/2019
Level of Funding:
Project Goals: 1) Discovery and nomination of novel molecular subtypes of prostate cancer; 2) Characterize associations of molecular subtypes of prostate cancer with clinical outcome and/or aggressiveness of disease in a radical prostatectomy cohort; 3) Characterize associations of molecular subtypes of prostate cancer with clinical outcome.
Specific Aims: Same as above
Role: Co-Investigator

OVERLAP: None

WU, Yi-Mi
CURRENT

5 P50 CA186786 **(Chinnaiyan)**
Title: **SPORE in Prostate Cancer, Project 1: A Precision Medicine Approach to Elucidate Mechanisms of Progression and Resistance to Therapy in Advanced Prostate Cancer**
Time Commitments: 10% effort, 1.20 calendar
Supporting Agency: NIH/NCI
Grants Officer: Andrew Hruszkewycz, Phone: 301-496-8528, hruszkea@mail.nih.gov
Performance Period: 09/11/2014-08/31/2019
Level of Funding:
Goals: 1) Discovery and nomination of novel molecular subtypes of prostate cancer; 2) Characterize associations of molecular subtypes of prostate cancer with clinical outcome and/or aggressiveness of disease in a radical prostatectomy cohort; 3) Characterize associations of molecular subtypes of prostate cancer with clinical outcome.
Specific Aims: Same as above
Role: Research Investigator

OVERLAP: None

What other organizations were involved as partners?

The Partnering PI, Dr. Arul Chinnaiyan, is from the University of Michigan. Drs. Chinnaiyan and Navone as well as the University of Michigan and MD Anderson teams worked closely to design and interpret the studies performed during the period of this progress report. Partnering PI performed all next-generation sequencing studies, made the results available in a timely manner, and provided the software and knowledge necessary for the MD Anderson team to interpret the next-generation sequencing results.

Partnering PI Location: The University of Michigan
1400 E. Medical Center Drive
5316 CCC
Ann Arbor, MI 48109-5940

SPECIAL REPORTING REQUIREMENTS
Not Applicable

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site.

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